Antiviral Therapy and Long-term Outcome for Hepatitis B Virus-related Hepatocellular Carcinoma after Curative Liver Resection in a Japanese Cohort

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Abstract. *Aim: The aim of this study was to determine whether antiviral therapy with nucleotide/nucleoside analog (NA) is beneficial for Japanese patients with hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC) who underwent initial curative liver resection. Patients and Methods: In 162 patients with positive hepatitis B surface antigen and negative anti-hepatitis C virus antibody, sixty-two patients received antiviral therapy with NA (NA group) and the remaining 100 patients did not (non-NA group). Prognostic factors for disease-free survival (DFS) and overall survival (OS) were evaluated. Moreover, to equalize the background covariates, a one-to-one propensity case-matched analysis was used. Results: NA administered were lamivudine (LAM) solely for 21 patients, LAM plus adefovir dipivoxil (ADV) for 6, LAM switched to entecavir (ETV) for 5 and ETV solely for 31. DFS did not significantly differ between the NA group and non-NA group (p=0.19). However, OS was significantly different (p=0.0063); 1-,3- and 5-year OS were 100% and 85.9%, 88.3% and 61.9% and 65.1% and 58.0%, respectively. In multivariate analysis, no antiviral therapy with NA was an independent poor prognostic factor (hazard ratio (HR)=2.72; p=0.0229). However, after propensity case-matched analysis, disease-free and overall survival were not significantly different between the two groups. Conclusion: In a Japanese cohort, antiviral therapy with NAs might provide longer survival for postoperative HBV-related HCC patients compared to patients without antiviral therapy. However, deterministic evaluation was impossible by this study alone.*

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Hepatocellular carcinoma (HCC) is the fifth most common cancer in the world and the third most common cause of cancer-related death (1-3). It has been estimated that more than 50% of HCCs worldwide are etiologically-associated with hepatitis B virus (HBV) infection and more than 80% of HBV-related HCCs are in developing countries (4, 5).

In Japan, the proportions of HBV-related HCC patients were constant, 15 to 20% (6) in the patients with HCC. As chronic HBV infection leads to liver cirrhosis or HCC development, published studies have shown that up to 25% of chronically-infected patients eventually die of liver cirrhosis or HCC. A review of the literature reveals that half of cases of HCC are attributable to persistent viral infections with HBV and HBV infection affects over 350 million people worldwide (7-8).

Hepatic resection can provide a potentially curative outcome for HCC patients who are indicated for this procedure (4, 9). However, long-term survival far from satisfying, with the main reason for high mortality attributable to tumor recurrence after resection, which is approximately 38 to 65% during the first 5 years (10-12). The prevention of recurrent HCC in patients after curative treatment is important in order to improve prognosis. With regard to HBV-related HCC, recent studies have evaluated

Table I. *Patients' characteristics in the two groups.*

Variable		Antiviral therapy with NA (n=62)	No antiviral therapy (n=100)	*p*-Value
Gender	Male	55 (89%)	84 (84%)	
	Female	7 (11%)	16 (16%)	0.4
Age (years)		55.2±1.28 (34-74)	59.7±1.00 (30-83)	0.006*
AST (IU/l)		36.1±4.3 (10-271)	31.9±1.5 (11-100)	0.28
ALT (IU/l)		41.0±4.4 (8-253)	32.1±1.9 (9-118)	0.39
Platelet count (104/mm^3)		14.5±2.8 (6.6-26.6)	18.6±2.1 (4.2-32.8)	0.3
ICGR15 (%)		9.9±0.9 (1-28.2)	11.1±0.7 (0.9-32)	0.27
Liver damage	A	57 (92%)	90 (90%)	
	B	5 (8%)	10 (10%)	0.53
HBV-DNA (log copies/ml)		3.8±0.3 (<2.6-7.6)	3.5±0.2 (<2.6-6.7)	0.38
Number of tumors		1.5±0.2 (1-4)	1.9±0.2 (1-14)	0.14
Maximum tumor diameter (mm)		37±5.0 (2-200)	57±4.0 (17-180)	0.002*
Type of resection	Major	14 (23%)	33 (33%)	
	Minor	48 (77%)	67 (67%)	0.16
Postoperative complications	Yes	10 (16%)	22 (22%)	0.36
Operating time (minute)		411±15 (210-720)	435±12 (111-775)	0.23
Intraoperative blood loss (g)		507±103 (5-3400)	881±81 (10-5027)	0.0049*
Resected liver volume (g)		266±39 (17-1800)	461±54 (15-1940)	0.0087*
F stage	F0-2	22 (35%)	42 (42%)	
	F3/4	40 (65%)	58 (58%)	0.17
A grade	A0/1	24 (39%)	51 (51%)	
	A2/3	38 (61%)	49 (49%)	0.1
Differentiation of tumor	well/mod	41 (66%)	65 (65%)	
	poor	21 (34%)	35 (35%)	0.95
Tumor stage	I/II	36 (58%)	44 (44%)	
	III/IV	26 (42%)	56 (56%)	0.23

Each characteristic is expressed as the mean±SD with range. Differences were considered significant if $p<0.05$*. Major resection was defined as resection of equal to or more than three segments. Postoperative complications were defined as a condition characterized as greater than Grade III of the Clavien-Dindo classification.

viral replication status, particularly HBV viral load as a predictor of good prognosis (13-16). Antiviral therapy with nucleotide/nucleoside analog (NA), including lamivudine (LAM), adefovir dipivoxil (ADV) and entecavir (ETV), has been reported to be beneficial in preventing progression to cirrhosis and development of HCC in patients with chronic hepatitis B (1, 7, 17-19). It has been several years from the introduction of the new NAs; ETV in Japan.

Recently, several studies from Asian countries, other than Japan, have published that perioperative antiviral therapy with NA improved the long-term outcome after resection of HBV-related HCC patients (4, 20, 21). However it is well-known that distributions of HBV genotype were different in Japan and the other countries. Although HBV genotype A has been increasing in Japan, predominantly through immoral sexual contacts, the percentage of HBV genotype A is still 3.5% and the majority of patients (82.2%) were in HBV genotype C (22). The severity of liver disease, response to antiviral therapies and HCC incidence differ according to the HBV genotype (23-26).

We conducted the present study to determine whether antiviral therapy with NA is beneficial for Japanese patients with HBV-related HCC who underwent initial curative liver resection. To decrease patients' selection bias in retrospective studies, we used multivariate analysis by Cox's proportional hazard model and a propensity case-matched analysis (27, 28).

Patients and methods

Patients. From January 2001 to March 2012, our surgical team performed 626 initial liver resections for HCC with macroscopically complete removal of the tumor and a pathologically tumor-free surgical margin. A total of 162 patients found to be positive for the hepatitis B surface antigen and negative for the anti-hepatitis C virus antibody were enrolled to the study. This study was approved by the institutional ethics committee of Kumamoto University Hospital and was performed in accordance with the 1975 Declaration of Helsinki. Written informed consent was obtained from all patients before treatment.

Indications for antiviral therapy. The serum HBV DNA concentration was measured using a polymerase chain reaction (PCR) assay (Amplicor HBV monitor assay; Roche Diagnostics, Manheim, Germany) and expressed as log copies/ml. Indications for antiviral therapy were performed basically based on the Japanese guideline of prevention and treatment for chronic hepatitis B (29): (i) for Hepatitis B e Antigen (HBeAg)-positive patients, the value of

Table II. *Univariate analysis of prognostic factors for overall survival.*

		Univariate analysis			
Variable		Number of patients	HR	95%CI	*p*-Value
Gender	Male	139			
	Female	23	1.38	0.65-2.66	0.38
Age (years)	<58	77			
	≥58	85	1.11	0.63-1.94	0.72
AST (IU/l)	<29	81			
	≥29	81	2.17	1.23-3.95	0.0070*
ALT (IU/l)	<30.5	80			
	≥30.5	82	1.83	1.03-3.37	0.040*
Platelet count	≥15.3	85			
($104/mm^3$)	<15.3	77	1.62	0.92-2.90	0.095
ICGR15 (%)	<10.15	87			
	≥10.15	75	1.32	0.75-2.36	0.33
Liver damage	A	147			
	B	15	3.37	1.58-6.56	0.0027*
HBV-DNA	<3.1	46			
(log copies/ml)	≥3.1	47	1.01	0.43-2.89	0.84
Antiviral therapy	Yes	62			
with NA	No	100	2.44	1.27-5.17	0.0063*
Number of	Single	96			
tumors	Multiple	66	2.52	1.42-4.52	0.0017*
Tumor diameter	<35	87			
(mm)	≥35	75	2.66	1.52-4.81	0.0006*
Postoperative	No	130			
complications	Yes	32	1.07	0.53-2.00	0.84
Operating time	<416.5	80			
(minute)	≥416.5	81	2.03	1.15-3.69	0.014*
Intraoperative	<418	79			
blood loss (g)	≥418	79	3.43	1.81-7.06	<0.0001*
Resection liver	<210	74			
volume (g)	≥210	71	1.88	1.05-3.50	0.035*
F-stage	F0-2	64			
	F3/4	98	1.64	0.85-3.35	0.14
A-grade	A0/1	75			
	A2/3	87	2.02	1.07-4.04	0.030*
Differentiation	well/mod	106			
of tumor	poor	56	1.14	0.63-2.19	0.42
Tumor stage	I/II	80			
	III/IV	82	3.40	1.86-6.58	<0.0001*

Cut-off value was defined as the median value. Differences were considered significant if $p<0.05$*. AST, Aspartate aminotransferase; ALT, alanine aminotransferase; ICGR15, indocyanine green retention rate at 15 min; HBV-DNA, hepatitis B virus- deoxyribonucleic acid; NA, nucleotide /nucleoside analog; F-stage, pathological fibrosis-stage; A-grade, pathological activity-grade

HBV DNA ≥10^5 copies/ml; or for HBeAg-negative patients, HBV DNA ≥10^4 copies/ ml; and alanine aminotransferase (ALT) ≥ two folds the upper limit of normal; (ii) for patients with compensated cirrhosis, HBV DNA ≥10^4 copies/ml for HBeAg-positive patients and HBV DNA ≥10^3 copies/ml for HBeAg-negative patients, with dose irrespective of the level of ALT; (iii) for patients with cirrhosis in the decompensation period who should receive antiviral therapy once HBV DNA is detected.

Table III. *Multivariate analysis of risk factors for poor overall survival.*

	Multivariate analysis		
Variable	HR	95%CI	*p*-Value
AST	1.12	0.46-2.79	0.80
ALT	1.78	0.65-5.28	0.27
Liver damage	3.40	1.19-9.33	0.023*
Number of tumors	2.16	1.04-4.57	0.039*
Tumor diameter	2.39	1.08-5.82	0.031*
Antiviral therapy with NAs	2.72	1.14-7.33	0.023*
Operating time	1.01	0.33-3.06	0.99
Intraoperative blood loss	1.51	0.51-5.13	0.47
Resected Liver volume	2.05	0.85-5.31	0.11
A-grade	1.07	0.45-2.55	0.87

Differences were considered significant if $p<0.05$*. AST, Aspartate aminotransferase; ALT, alanine aminotransferase; A-grade, pathological activity-grade

Hepatic resection. The type of hepatectomy was selected based on the tumor size and location, extent of the tumor invasion, functional liver volume and the patients' general condition as described previously (30, 31). If the liver function allowed, anatomical resection was employed. In patients with insufficient liver functional reserve, limited resection was performed. Major resection was defined as resection of equal to or more than three segments. Postoperative complications were defined as a condition characterized by equal or over Grade III of Clavien-Dindo classification (32).

Data collection. The following data were prospectively collected in a prospective database; gender, age (years), aspartate aminotransferase (AST) and ALT, platelet count, indocyanine green retention rate at 15 min (ICG R15), degree of liver damage (A to C), HBV-DNA (copies/ml), tumor number, maximum tumor diameter (mm), type of resection, postoperative complications, operating time (minutes), intraoperative blood loss (ml), percentage of red cell concentrates (RCC) transfused and fresh frozen plasma (FFP) administered, resected liver volume (g), pathological fibrosis (F)-stage and activity (A)-grade by the Inuyama classification (33), tumor differentiation and tumor staging (34) and the date of recurrence and death.

Follow-up. After hepatic resection, all of the patients underwent regular follow-up examinations of tumor markers (serum alpha-fetoprotein (AFP), lens culinaris agglutinin-reactive fraction of AFP (AFP-L3) and des-c-carboxy prothrombin (DCP) levels) (35), while ultrasonography (US) and enhanced computed tomography (CT) or magnetic resonance imaging (MRI) studies were undertaken every 2-4 months to detect any intrahepatic and extrahepatic metastasis (36). When tumor recurrence was confirmed in the remnant liver, various treatment modalities were selected, including repeat hepatectomy, radiofrequency ablation, transcatheter arterial chemoembolization, chemotherapy with sorafenib or a combination of these methods.

Table IV. *Patients' characteristics in the two groups after propensity analysis.*

Variable		Antiviral therapy with NAs (N=46)	No antiviral therapy group (N=46)	*p*-Value
Gender	Male	40 (87%)	39 (85%)	
	Female	6 (13%)	7 (15%)	0.45
Age (years)		56.8±1.5 (34-74)	58.2±1.5 (30-77)	0.53
AST (IU/l)		37.3±5.7 (10-271)	31.2±2.2 (11-100)	0.32
ALT (IU/l)		37.5±5.5 (8-253)	35.7±2.9 (11-95)	0.77
Platelet count (104/mm3)		14.6±0.9 (6.6-37.7)	15.9±0.7 (5.4-29)	0.27
ICGR15 (%)		10.0±0.8 (1-23)	10.6±1.0 (0.9-32)	0.68
Liver damage	A	41 (89%)	43 (93%)	
	B	5 (11%)	3 (7%)	0.46
HBV-DNA (log copies/ml)		3.8±0.3 (<2.6-7.6)	3.5±0.2 (<2.6-6.7)	0.38
Number of tumors†		1.6±0.1 (1-4)	1.8±0.2 (1-5)	0.37
Maximum tumor diameter (mm) †		41±5.1 (2-200)	38±3.5 (2-105)	0.57
Type of resection	Major	12 (26%)	8 (17%)	
	Minor	34 (74%)	38 (83%)	0.31
Postoperative complications	Yes	9 (20%)	8 (17%)	0.79
Operating time (minute)		421±16 (210-675)	419±19 (204-775)	0.95
Intraoperative blood loss (g)		514±85 (20-3400)	764±119 (10-3600)	0.09
resected liver volume (g)		293±49 (20-1800)	277±49 (15-1440)	0.82
F stage	F0-2	14 (33%)	17 (43%)	
	F3/4	28 (67%)	22 (57%)	0.34
A grade	A0/1	17 (40%)	23 (59%)	
	A2/3	25 (60%)	16 (41%)	0.1
Differentiation of tumor	Well/mod	15 (33%)	14 (30%)	
	poor	31 (67%)	32 (70%)	0.82
Tumor Stage	I/II	24 (52%)	27 (59%)	
	III/IV	22 (48%)	19 (41%)	0.53

Each characteristic is expressed as the mean±SD with range. Differences were considered significant if $p<0.05^*$. Major resection was defined as resection of equal to or more than three segments. Postoperative complications were defined as a condition characterized by greater than Grade III according to Clavien-Dindo classification.

Statistical analysis. Quantitative and qualitative variables are expressed as the mean±standard deviation, median and range and frequency. Data were compared between the two groups using the Student's *t*-test and Chi-square test. Categorical variables were compared using the Chi-square test or Fisher's exact test. Disease-free survival (DFS) and overall survival (OS) were calculated using the Kaplan-Meier method and compared with the log-rank test. After the univariate analysis, significant variables were used in the multivariate analysis using the Cox proportional hazard model. Statistical analyses were performed using the JMP program (SAS Institute, Cary, NC, USA). Differences were considered significant if $p<0.05$.

A propensity score analysis (27, 28) was used to build a matched group of patients for comparison of clinical outcomes and long-term survival between antiviral therapy with NA and without. Logistic regression analysis was applied to generate a continuous propensity score ranging from 0 to 1. One-to-one matching without replacement as performed by 0.01 caliper-matching on the estimated propensity score generated 46+46 matched antiviral therapy groups with NA and without.

Results

Among 162 patients enrolled, 62 received antiviral therapy with NA preoperative or postoperative situation (NA group) and the remaining 100 never received antiviral therapy with NA (non-NA group) (Figure 1). In the NA group, treatment with LAM was started in 31 patients; ADV was administered concurrently to 6 patients and LAM was switched to ETV in 5 patients. In the remaining 31 patients, ETV was used as the initial treatment. NA administration was started before and after hepatic resection in 24 and 38 patients, respectively.

Background characteristics. Background characteristics of 162 patients with or without antiviral therapy are demonstrated in Table I. Patients in the NA group showed significantly younger age, smaller tumor size, reduced intraoperative blood loss and smaller resected liver volume (Table I).

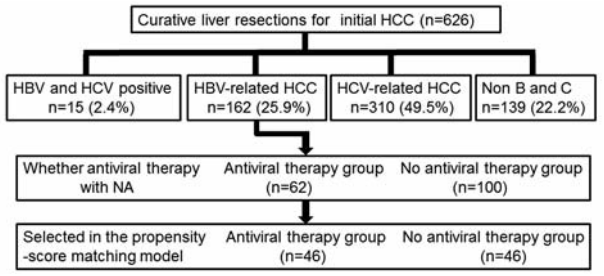


Figure 1. *Distribution of patients according to initial curative liver resections for HCC. In all, 162 patients (25.9%) were positive for the hepatitis B surface antigen and 62 patients received antiviral therapy with NAs; 46 pairs of matched patients were selected for the propensity model.*

Comparison of DFS and OS in receiving antiviral therapy. The median follow-up duration in DFS and OS was 495 days (range=22-2.422 days) and 976 days (range=22-3.374 days) in the NA group and 369 days (range=7-3.388 days) and 1.008 days (range=9-3.836 days) in the non-NA group. The DFS and OS curves of two groups are shown in Figure 2 (A and B). There were no differences in DFS (p=0.19); however, in OS, a significant difference was identified between the two groups (p=0.0063). Median DFS and OS of the non-NA group (n=100) was 11.9 and 32.5 months. Median DFS and OS of the NA group (n=62) was 16.0 and 31.5 months. In the NA and non-NA group, the 1-, 3- and 5-year DFS were 76.8% and 57.6% , 42.8% and 38.7% and 38.9% and 34.5%, respectively and the 1-, 3- and 5-year OS were100% and 85.9%, 88.3% and 61.9% and 65.1% and 58.0% , respectively.

Prognostic factors for OS. Univariate analyses for prognostic factors of OS after curative resection of HBV-related HCC are shown (Table II). Univariate analyses revealed that AST, ALT, degree of liver damage, multiple tumors, maximum tumor size >35 mm, operating time, intraoperative blood loss, resected liver volume, liver damage A grade, tumor staging and antiviral therapy with NA were associated with OS. Multivariate analyses revealed that liver damage B, multiple tumors, maximum tumor size >35 mm and no antiviral therapy with NA were independently associated with poorer OS (Table III). Notably, no antiviral therapy with NA was confirmed to be independently related to poor survival outcome (hazard ratio (HR)=2.72; 95% confidence interval (CI)=1.14-7.33, p=0.023).

Prognostic factors for DFS. Univariate analyses revealed that platelet count, degree of liver damage, multiple tumors, maximum tumor size >35 mm, operating time, intraoperative blood loss and resected liver volume were associated with DFS after curative resection of HBV-related HCC. Antiviral therapy with NA was not associated with DFS.

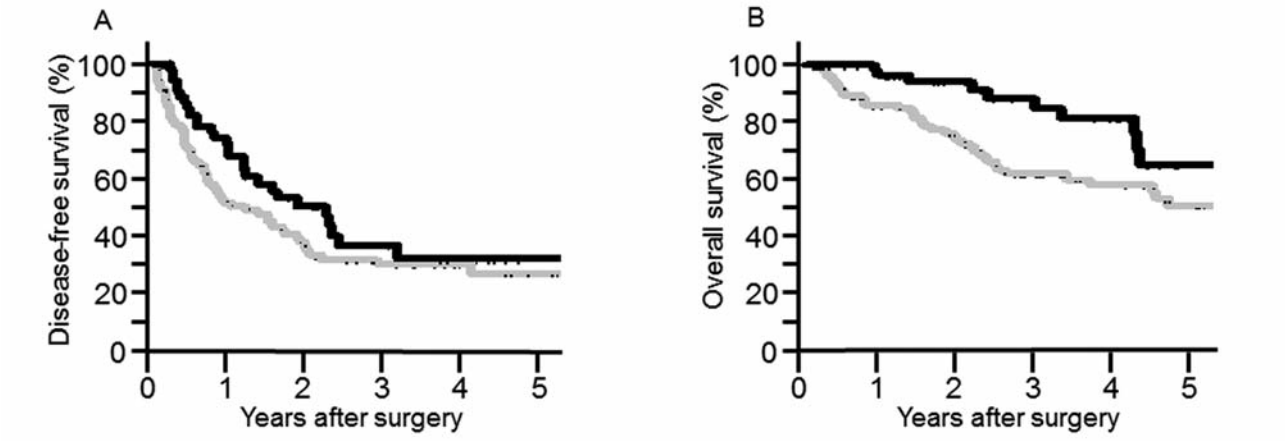
Comparison of DFS and OS by kind of NA. We also compared DFS and OS between the group of LAM (n=26) and ETV (n=31). The DFS and OS curves of two groups are shown (Figure 3A and 3B). There were no significant differences between the two groups (p=0.15 and p=0.61). Median DFS and OS of the LAM group was 21.5 and 54.6 months. Median DFS and OS of the ETV group was 13.8 and 23.5 months. The estimated 1-, 3- and 5-year DFS for the LAM and ETV group were 79.3% and 71.3%, 52.6% and 24.8% and 52.6% and 16.5%, respectively (Figure 2A). The estimated 1-, 3- and 5-year OS for the LAM and ETV group were 87.7% and 80.7% , 83.0% and 74.5% and 83.0% and 74.5%, respectively (Figure 2B).

Comparison of DFS and OS after propensity score analysis. Five out of 18 covariants; gender, HBV DNA, ALT, maximum tumor diameter and envelope integrity, in baseline characteristics before matching, were unbalanced by logistic regression analysis (p<0.05). After propensity score-matching, the covariants were all balanced (Table IV). After propensity score analysis, there were 46 patients in each group. The median follow-up duration in DFS and OS was 483 days (range=22-3.374 days) and 1,018 days (range=22-3.374 days) in the NA group and 429 days (range=9-2.905 days) and 1009 days (range=9-3.836 days) in the non-NA group. The DFS and OS curves of two groups are shown in Figure 4A and 4B. There were no significant differences in DFS and OS between the two groups (p=0.45 and p=0.36).

Discussion

A high serum concentration of HBV DNA (≥4 $\log_{10}$ copies/ml) was an independent risk factor for OS and recurrence-free survival (RFS) in a prospective cohort study (4), a randomized control trial (RCT) (20) and propensity score-matching study (21) in Asian countries, as well as a retrospective cohort study in Japan (1). To prevent postoperative recurrence, antiviral therapy should be initiated in patients with hepatitis B virus DNA≥4 $\log_{10}$ copies/ml (1, 4, 20, 21). When we divided the NA group patients into the two groups according to the median value of HBV-DNA (3.1 $\log_{10}$ copies/ml), there were no significant differences in OS and DFS. In fact, antiviral treatment clearly significantly decreased HCC recurrence with HRs of 0.48 and 0.50 and HCC-related death with HRs of 0.26 and 0.49 (4, 20). In the current study, although OS was significantly better with a HR of 0.37 treated with antiviral therapy, DFS did not show any significant differences by multivariate analysis. Unfortunately, the propensity-matching cohort did not demonstrate any advantages in OS and DFS.

Remnant liver function is an important factor of therapeutic strategy and is the most important prognostic factor (37, 38). It is considered that liver function has been improved by the administration of NA and the cause of death



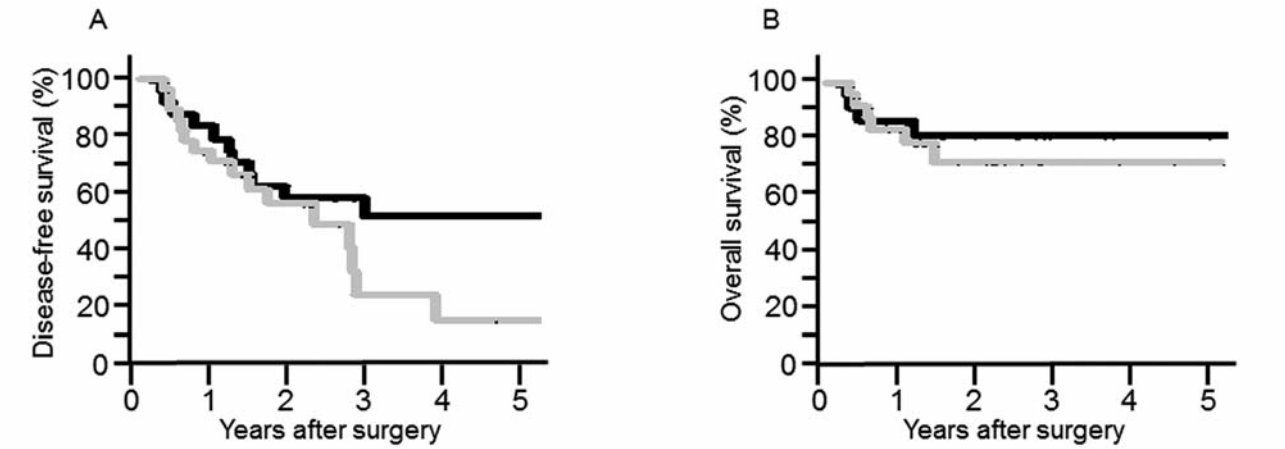
Number at risk

Years	0	1	2	3	4	5
Antiviral therapy	62	41	25	13	10	5
No antiviral therapy	100	51	37	26	19	14

Number at risk

Years	0	1	2	3	4	5
Antiviral therapy	62	54	39	29	23	13
No antiviral therapy	100	74	65	46	30	27

Figure 2. *Disease-free survival (DFS) and cumulative overall survival (OS) rates in all patients in the no-antiviral-therapy group and antiviral-therapy group. Grey line, no antiviral therapy group; black line, antiviral therapy group.*



Number at risk

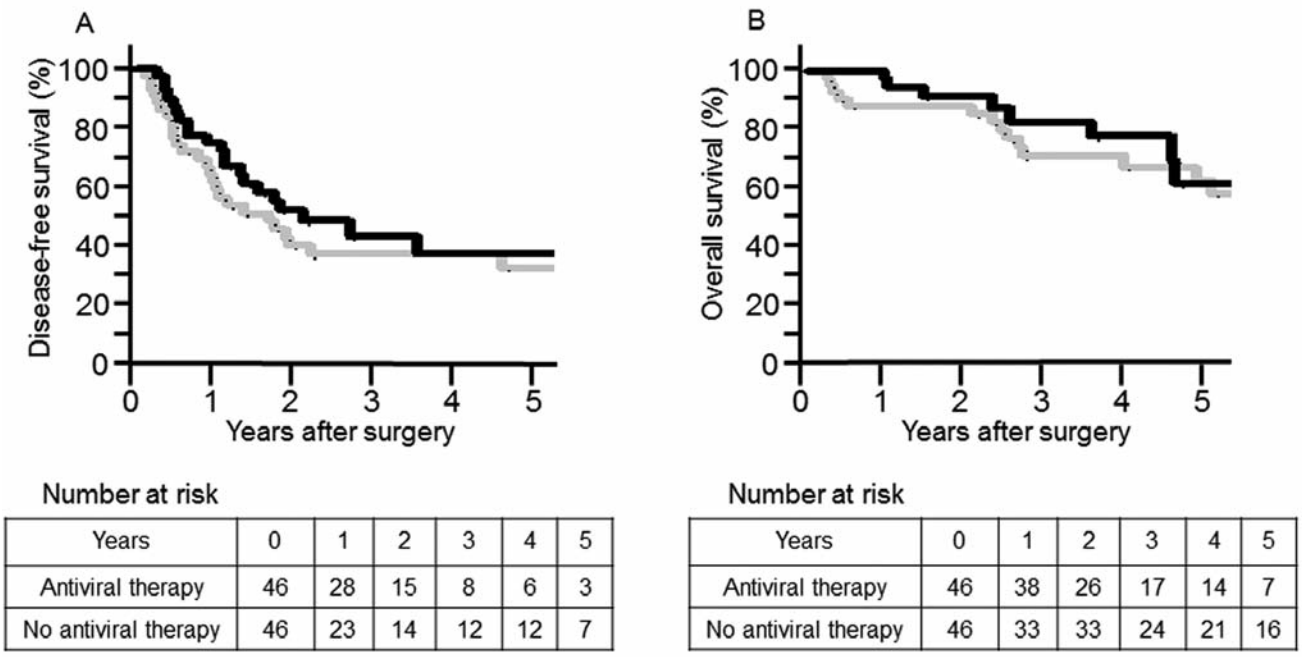
Years	0	1	2	3	4	5
LAM group	26	19	14	9	7	5
ETV group	31	18	10	3	2	1

Number at risk

Years	0	1	2	3	4	5
LAM group	26	19	14	9	7	5
ETV group	31	19	10	3	2	1

Figure 3. *Disease-free survival (DFS) and cumulative overall survival (OS) rates in all patients in the LAM and ETV group. Grey line, ETV group; black line, LAM group.*

due to liver failure decreased. In addition, by improving liver function, it is considered possible that when the patients relapse, an adequate treatment, including hepatic resection, can be performed. Administration of NA was reported to decrease both tumor- and liver-related mortality (4). The differences in the proportion of HBV genotype in Japan and the other countries may influence the response to antiviral therapies (23-26).



Number at risk

Years	0	1	2	3	4	5
Antiviral therapy	46	28	15	8	6	3
No antiviral therapy	46	23	14	12	12	7

Number at risk

Years	0	1	2	3	4	5
Antiviral therapy	46	38	26	17	14	7
No antiviral therapy	46	33	33	24	21	16

Figure 4. *Comparison of survival curve between the two groups after propensity score-matching. Black line, antiviral therapy with NAs group (n=46); Grey line, without antiviral therapy group (n=46). A, disease-free survival; B, overall survival.*

Lately, established NAs have been demonstrated to inhibit HBV replication, reduce hepatitis and improve histological findings in background liver. They have also been proven to inhibit progression to cirrhosis and HCC (39). In the present study, there was no significant difference in prognosis between the LAM and ETV groups. Ten patients of the LAM group (n=26) were treated with LAM and ADV combination therapy. Urata and Kubo *et al*. (12) reported that LAM may potentially prevent HCC recurrence after curative resection of HBV-related HCC and, recently, Urata *et al*. (1) demonstrated that ETV may have long-term outcomes after curative resection for HCC in patients with a high serum concentration of HBV-DNA. ETV is well-known to result in a better virological response and lower drug-resistance compared to LAM (40, 41). However, another study suggested that combination therapy of LAM and ADV was superior to ETV-alone in re-treatment of patients with failure therapy of LAM (42), whereas another study showed that LAM and ADV combination therapy had a lower risk of developing genotypic resistance to ADV (43).

In conclusion, antiviral therapy might improve long-term outcome after curative hepatic resection for Japanese HCC patients with HBV-DNA; however, the effect observed was not confirmed by propensity score-matching analysis. Therefore, a larger prospective investigation assessing HBV genotype will be required.

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